Small intestinal presentation of nodular lymphocyte-predominant Hodgkin lymphoma with T cell/histiocyte-rich B cell lymphoma-like areas—with review of literature on extranodal presentation of this disease

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Abstract Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), accounts for ~5% of all cases of Hodgkin lymphoma and is characterized by involvement of the peripheral lymph nodes. NLPHL occurs in young adults and is associated with frequent relapses. In 3% to 7% of cases, NLPHL progresses to a diffuse large B cell lymphoma. Furthermore, a proportion of NLPHL also have areas with features of T cell/histiocyte-rich large B cell lymphoma (THRLBCL), either at presentation or on follow-up. Here, we describe a 32-year-old man who presented to the emergency department with small bowel perforation. The resected small bowel showed full-thickness mural ulceration and involvement by a lymphoma with features of NLPHL that also had areas resembling THRLBCL. The patient had axillary lymphadenopathy, biopsy of which showed NLPHL with focal THRLBCL-like areas. Such a lymphoma presenting as small intestinal lesion/perforation has not been reported in the literature before. We take this opportunity to review the literature on

extranodal presentations of NLPHL and discuss the natural history of this disease.

Keywords Lymphoma · Hodgkin lymphoma · Diffuse large B cell lymphoma · Gray zone lymphoma · Immunohistochemistry

Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is an uncommon disease accounting for about 5% of all cases of Hodgkin lymphoma (HL) in Western countries. It is characterized by a nodular/large-follicular pattern and neoplastic proliferation of abnormal large B cells (popcorn cells) that are currently termed lymphocyte-predominant cells (LP cells), in a germinal center-like microenvironment. NLPHL typically affects adults in the third to fifth decades of life, and has an indolent clinical course with fairly frequent relapses. NLPHL involves peripheral nodes, and unlike classical HL (cHL), mediastinal and splenic involvement are rare. Recurrences of cHL usually show features of cHL, whereas recurrences of NLPHL can show either NLPHL or transformation to a large B cell lymphoma. In approximately 3–7% patients with NLPHL, concurrent or subsequent transformation to a diffuse large B cell lymphoma (DLBCL) is observed [1–4]. A clonal relationship has been demonstrated between the LP cells of NLPHL and the neoplastic large B cells of the associated DLBCL by molecular genetics [1, 6–8].

T cell/histiocyte-rich large B cell lymphoma (THRLBCL) represents a variant of diffuse large B cell lymphoma (DLBCL) which was first described in 1988 by Ramsay et

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al. THRLBCL is characterized by a diffuse pattern, and the neoplastic CD20 positive B cells account for less than 10% of the infiltrate and are scattered among a majority of non-neoplastic T cells with or without histiocytes [4, 5]. THRLBCL is commonly confused with peripheral T cell lymphoma and HL, especially NLPHL. Furthermore, a proportion of NLPHL, more commonly at recurrence, have THRLBCL-like areas, and these need to be distinguished from primary THRLBCL. As per the current criteria, presence of a single nodule with features of NLPHL in otherwise diffuse infiltrate with THRLBCL-like appearance would exclude the diagnosis of primary THRLBCL [9]. Patients of NLPHL with THRLBCL-like areas present at a higher stages and with B symptoms, but still have an excellent survival similar to conventional NLPHL [10].

A feature common to both NLPHL and THRLBCL is the fact that both, in an overwhelming majority of cases, present with lymph nodal involvement. Extranodal presentation of NLPHL is almost unknown. Rare lung involvement at presentation has been reported [11]. Involvement of spleen (8%), liver (3%), bones (2%), and lung (1%) during the course of the disease has been reported [12]. On the other hand, nearly one half of patients with THRLBCL present with liver, bone marrow, and/or spleen involvement [1]. In addition, primary cutaneous, ethmoidal sinus, and meningeal presentations of THRLBCL are documented [13–15]. Only one case of an ileal presentation of THRLBCL is reported [5].

In this report, we document a case of NLPHL with THRLBCL-like areas presenting in the small intestine. Both components could be documented in the intestine and was further supported by a lymph node biopsy performed later. To the best of our knowledge, such a case has not been reported earlier.

Material and methods

Clinical history A 32-year-old male was being investigated for fever and axillary lymphadenopathy when he presented with acute abdomen. At laparotomy, he was found to have small bowel perforation, and he underwent a small bowel resection. Following his recovery from the surgical procedure, he underwent an excision biopsy of the enlarged right axillary lymph node.

Immunohistochemistry Four-micron-thick sections cut from the paraffin blocks were investigated for immunohistochemistry. The slides were immunostained with antibodies to CD45 (DAKO; dilution 1:10; antigen retrieval 20 min MW, EDTA pH 8.0), CD20 (DAKO; dilution 1:250; antigen retrieval 20 min MW, citrate pH 6.0), CD30

(DAKO; dilution 1:50; antigen retrieval 20 min MW, Dako retrieval solution pH 6.0), CD15 (DAKO; dilution 1:10; antigen retrieval 20 min MW, citrate pH 6.0), BCL6 (DAKO; dilution 1:20; antigen retrieval 20 min MW, EDTA pH 8.0), BOB-1 (Novacastra; dilution 1:50; antigen retrieval 20 min MW, citrate pH 6.0), OCT-2 (Novacastra; dilution 1:50; antigen retrieval 20 min MW, citrate pH 6.0), and P53 (Novacastra; dilution 1:50; antigen retrieval 10 min MW, citrate pH 6.0), ALK (DAKO; dilution 1:10; antigen retrieval 20 min MW, Dako retrieval solution pH 9.9), pan-T cell antigens (CD3, CD2, CD7, and CD5; all from Novacastra; dilution 1:50; antigen retrieval 20 min MW, EDTA pH 8.0), CD57 (Becton Dickinson; dilution 1:40; antigen retrieval 20 min MW, citrate pH 6.0), CD4 (Novacastra; dilution 1:400; antigen retrieval 20 min MW, EDTA pH 8.0), CD8 (Novacastra; dilution 1:50; antigen retrieval 20 min MW, EDTA pH 8.0), CD68R (DAKO; dilution 1:50; antigen retrieval 20 min MW, citrate pH 6.0), and CD21 (DAKO; dilution 1:50; trypsin 15 min). In situ hybridization using the Epstein Barr virus (EBV) encoded small RNA probe (EBER; Vision Biosystems Newcastle upon Tyne, UK; Novacastra, Newcastle upon Tyne, UK) was undertaken to detect EBV association.

Results

Small bowel perforation Sections from the small bowel perforation showed full-thickness ulceration and perforation of the small bowel wall with purulent exudate on the mucosal aspect and a fibrinous/purulent exudate on the serosal surface. On one side, adjacent to the perforated area,

Fig. 1 Section from the site of small bowel perforation. On the right side of the perforated area, a dense vaguely nodular infiltrate of small lymphoid cells is noted (NLPHL component). On the left side of the perforation, the infiltrate is less dense and more polymorphic (THRLBCL-like component; X12.5)

a dense infiltrate of small lymphoid cells with occasional scattered larger cells was noted. A vague large nodular pattern was discernible. On the other side of the perforation, the infiltrate was less dense, and there was an admixture of small lymphoid cells with histiocytic cells, and the larger cells amounted to 5–10% of the infiltrate. The surrounding mucosa did not show significant abnormalities except for occasional foci with increased numbers of intra-epithelial lymphocytes (Figs. 1 and 2).

The larger lymphoid cells expressed CD45, CD20, BCL6, BOB-1, OCT-2, and P53 and were negative for CD30, EBER, and ALK. In the area of dense lymphoid infiltrate, the small lymphoid cells were an admixture of B cells (CD20 positive) and T cells (CD3, CD2, CD7, and CD5 positive). A good proportion of these small lymphoid cells also expressed CD57. In the area with less dense infiltrate, most of the small lymphoid cells were T cells. The CD4/CD8 ratio was approximately 1:1 (Table 1). The

histiocytic cells expressed CD68R. CD21 stain showed follicular dendritic cell (FDC) meshworks in the nodular areas with a dense lymphoid infiltrate and lack of FDCs in the foci with a less dense lymphoid infiltrate (Fig. 3).

Two of the seven mesenteric lymph nodes showed paracortical expansion by an infiltrate of small to intermediate sized lymphoid cells, histiocytic cells, and an occasional larger lymphoid cell. The two lymph nodes were considered to be focally involved by the neoplasm.

Overall, the intestinal lymphoid infiltrate has features of NLPHL with THRLBCL-like areas. The NLPHL component was recognized in retrospect after the subsequent axillary lymph node biopsy was evaluated.

Right axillary lymph node biopsy The lymph node had a large nodular pattern. Most nodules were cellular without any fibrous septae and were composed of small lymphoid cells, histiocytic cells, and larger atypical cells. The large

Fig. 2 The figure highlights morphology and immunophenotype in the NLPHL component. Figures **a** (X100) shows an indistinct nodular pattern and **b** (X400) shows a dense infiltrate of small lymphoid cells with occasional larger LP cells. Figures **c** (X100) shows presence of

FDC meshworks on the CD21 immunostain and **d** (X400) represents CD20 immunostain showing larger LP cells and smaller B cells in the background

Table 1 Immunophenotype of small lymphoid cells in the intestinal lymphoid lesion

Antibody	Area with a high density of lymphoid cells (NLPHL)	Area with a low density of lymphoid cells (THRLBCL-like areas)
CD20	Positivity in a good number of small cells (B cells)	Almost no small B cells
CD2/CD3/CD5/ CD7	Positivity in a proportion of small cells	Almost all small cells were T cells
CD4/CD8	>5:1	About 1:1
CD57	Positivity seen in a good number of cells	Positive cells not significant

The large lymphoid cells in both areas were positive for CD45, CD20, BCL6, OCT-2, BOB.1, and P53 and negative for T cell markers, CD30, ALK, CD68R, and EBV

cells varied in morphology—centroblast-like cells, LP cells, and mononuclear Hodgkin-like cells. Plasma cells were scanty, and eosinophils were not seen. The proportion of large cells was variable. In some nodules, the large cells were seen in sheets with very few small lymphoid cells between.

The large cells expressed CD45, CD20, CD79a, BCL6, BOB-1, OCT-2, P53, and focally BCL2. They were negative for CD30, CD15, EBER, and ALK. Most of the small lymphoid cells were positive for CD2, CD3, CD4, CD7, and CD5. A good proportion of cells expressed CD57. CD8 positive cells were few. Most nodules also had

Fig. 3 The figure represents morphology and immunophenotype of the THRLBCL-like component. Figures **a** (X100) and **b** (X400) show a diffuse polymorphic infiltrate of cells with presence of large lymphoid cells in a mixed background of histiocytes, smaller

lymphoid cells, and some granulocytes. The CD20 immunostain in figure **c** (X200) shows scattered larger B cells and the CD8 immunostain in figure **d** (X100) demonstrates prominence of CD8-positive cells among the small lymphoid population

a good number of small B cells. However, in areas with syncytial clusters of large cells, small B cells were almost absent. CD21 and CD23 positive FDC meshworks were seen in an occasional nodule.

The lymph node was interpreted as a NLPHL with THRLBCL-like areas.

Discussion

In 1994, the Revised European-American Classification of Lymphoid Neoplasms (REAL classification) proposed nodular lymphocyte predominant Hodgkin's disease as morphologically, biologically, and clinically distinct from other types of Hodgkin's disease (HD), which were collectively termed classical HD [16]. This distinction between NLPHL and cHL is maintained in the current WHO classification [9]. It is well-recognized that DLBCL develops in 3–7% patients of NLPHL. In about one third of patients both components occur concomitantly. There has been a paucity of studies to address the issue of clinical outcome in these patients. Most reports in the literature include single case reports or small case series. Some of these suggest that DLBCL arising from NLPHL have a more indolent clinical course with a favorable outcome. However, the study from Nebraska suggested that such cases have an aggressive disease course and a poor long-term survival [2, 17–20].

Primary extranodal NLPHL is very rare. Involvement of extranodal sites occurs in about 15% of NLPHL patients. They include spleen, liver, bone, bone marrow, Waldeyer's ring, lungs, salivary gland, skin, and soft tissues. Often, these cases are advanced and present at multiple sites. A case with colonic involvement has been reported. This case showed full-thickness colonic wall necrosis, and the viable foci in the adjacent tissue showed NLPHL. Similar to other cases with extranodal involvement, this patient also had extensive disease with involvement of spleen and liver and abdominal, retroperitoneal, and celiac lymphadenopathy [10, 21, 22].

Extranodal presentation of NLPHL with THRLBCL-like areas, in small bowel with perforation, as seen in the present case has not been previously reported. Ulceration and necrosis further complicated the morphology. A variety of inflammatory conditions entered the differential diagnosis. It should be noted that in an intestinal perforation secondary to an inflammatory pathology, acute/histiocyte-rich inflammatory infiltrate and not a lymphoid infiltrate would be prominent. In addition, a lymphoma with a prominent T cell component in the small intestine needs to be differentiated from the more common enteropathy associated T cell lymphoma. Presence of CD20 positive large cells amidst CD8-positive small T cells should lead to the correct diagnosis in such a case.

The nodules of NLPHL represent transformed abnormal germinal centers and appropriate markers (CD21, CD23, or CD35) highlight the FDCs. In 2003, Fan and colleagues described six distinct immuno-architectural patterns of NLPHL-classic B cell-rich nodular, serpiginous nodular, nodular with prominent extranodal L&H cells, T cell-rich nodular, diffuse (THRLBCL-like), and (diffuse) with a B cell-rich background. A pure diffuse pattern and a nodular pattern with many extranodal LP cells have potential clinical significance, and diffuse pattern is an independent predictor of recurrence. Presence of extranodal LP cells is thought to represent early evolution to diffuse pattern [1].

The current case is the first reported case of small intestinal presentation of NLPHL or NLPHL with THRLBCL-like areas. The histology of our case caused diagnostic difficulties and a variety of inflammatory pathologies were considered at initial evaluation. However, careful morphological and immunohistochemical evaluation helped to reach the correct diagnosis. Furthermore, the case illustrates that the possibility of lymphoma should be considered in a perforated intestine if the intestinal wall shows excess of lymphoid cells even if these lymphoid cells appear small and innocuous.

Conflict of interest The authors declare that they have no conflict of interest.

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